Peripheral artery disease in the lower limbs

The importance of secondary risk prevention for improved long-term prognosis

SJ Aitken

Background
Patients with lower limb peripheral artery disease (PAD) are at high risk of cardiovascular mortality and morbidity along with limb loss. PAD is underdiagnosed in the community and presents a missed opportunity to prescribe evidence-based secondary prevention therapy.

Objective
The aim of this article is to summarise key updates in the management of patients with PAD, with particular reference to newly published guidelines.

Discussion
PAD continues to be a major contributor to the mortality and morbidity of patients with atherosclerosis in Australia. For patients with chronic limb-threatening ischaemia, revascularisation remains the mainstay of limb salvage, and expedited access to vascular surgery assessment is necessary. Both prescription of, and adherence to, evidence-based secondary prevention therapy is low. A greater emphasis on cardiovascular risk factor modification for all patients with PAD is required to improve long-term outcomes. General practitioners and vascular surgeons can work collaboratively to provide patient-centred, effective care to patients with PAD.

Vascular causes of lower limb problems are common. General practitioners (GPs) are ideally positioned to identify and help manage patients at risk of peripheral artery disease (PAD). PAD refers to atherosclerotic changes occurring in the aorta and the iliac and lower extremity arteries. It is associated with significant reduction in life expectancy and quality of life (QoL). Adverse outcomes are mainly due to cardiovascular morbidity and lower limb events. Recently, three collaborative international guidelines on PAD have been published: the Global Vascular Guidelines,1 the European Society of Vascular Surgery/European Society of Cardiology Guideline2 and the American Heart Association/American College of Cardiology Guideline.3 These include revised standards of care that re-emphasise PAD as a major contributor to the overall burden of cardiovascular disease.1–3

The aim of this article is to summarise the newly updated evidence relating to the diagnosis and treatment of lower extremity PAD.

Prevalence and classification of PAD
Despite significant improvements in the treatment of PAD, the overall prevalence of PAD in Australian patients remains high.4 Globally, PAD affects >200 million people.5 In Australian primary care settings, up to 10% of patients have a diagnosis of PAD.5 As patients age, PAD incidence increases, with 22% of Australians aged >75 years diagnosed with PAD.6,7

PAD is traditionally classified using the Rutherford or Fontaine classification as asymptomatic, intermittent claudication or critical limb ischaemia, using a combination of symptoms, signs and perfusion parameters such as the ankle brachial index (ABI), toe pressures or pulse volume.1 The Global Vascular Guidelines recommend the term ‘chronic limb-threatening ischaemia’ (CLTI) replaces the former ‘critical limb ischaemia’.1 This new term seeks to distinguish between acute and chronic ischaemia, and address the increasing contribution of diabetes-related foot disease to limb loss. CLTI does not include perfusion parameters as a diagnostic criterion, recognising that amputation risk is often a combination of ischaemia, tissue loss and infection.

Risk factors and complications of PAD
The risk factors for PAD are similar to the risk factors for cardiovascular disease. Smoking is one of the greatest risks for PAD, with those currently smoking at higher risk than non-smokers. A history of cardiovascular disease is also a significant contributor to PAD risk. Other risk factors,
such as hypertension, diabetes and hypercholesterolaemia, contribute to the cumulative risk of PAD.

The identification of patients with PAD is important because of the increased risk of cardiovascular and lower limb morbidity and mortality. Patients with PAD have a 3–4-fold increased risk of acute myocardial infarction (AMI) and a 10–15 times greater risk of cardiovascular mortality when compared with those without PAD. In the REduction of Atherosclerosis for Continued Health (REACH) registry, the incidence of major cardiovascular events at one year was 15% in patients with coronary or cerebral artery disease, compared with 21% in patients with PAD, indicating a one-third higher incidence in patients with PAD. These findings translate to significant adverse outcomes for patients.

PAD results in significantly lower QoL for patients. Patients with intermittent claudication have reduced QoL when compared with healthy patients; QoL is further reduced in patients with CLTI. Patients with CLTI report pain and impairment in physical function, emotional wellbeing and social interactions, which is similar to the health status of very ill patients with cancer. Disease progression is more likely in patients who are older, have an abnormal ABI, continue to smoke, and have diabetes or concurrent cardiovascular disease. At five years, 7% of patients with asymptomatic PAD have clinical deterioration, while 21% of patients with intermittent claudication have a reduction in walking distance or progress to CLTI. Long-term amputation rates are highly variable, with a large meta-analysis finding that incidence ranged between 4% and 27%, influenced by other risks such as infection and diabetes-related foot disease.

In particular, CLTI carries an extremely poor prognosis. In large population-based cohort studies, one-year mortality from CLTI ranged from 20% to 25%, and was up to 40–50% at five years. In NSW, patients with CLTI undergoing revascularisation procedures had four times the risk of amputation and almost double the risk of death at two years when compared with patients without CLTI after adjusting for age, comorbidities, sex and perioperative complications.

There are inequities in the presentation, diagnosis and treatment of PAD. Older patients are at particular risk of PAD but can face barriers to diagnosis as a result of lack of mobility, cognitive impairment or frailty. Aboriginal and Torres Strait Islander people have higher rates of amputation and a higher risk of cardiovascular morbidity following PAD intervention than non-Indigenous populations. Similarly, patients residing in rural and regional areas of Australia have higher amputation rates than those in metropolitan centres. While current statistics indicate that women are less affected by PAD, a recent review by Teodosescu et al of prevailing literature suggests that PAD may be systematically underdiagnosed in women, rather than there being a truly lower incidence.

The PAD population continues to be underdiagnosed and undertreated for cardiovascular risk factors. Risk factor modification and medical prescribing remains poor, especially for patients with CLTI. There is a need for good partnership between GPs and vascular surgeons to work together to address the needs of this high-risk group of patients.

### Clinical presentation of PAD

The diagnosis of PAD is often challenging (Table 1). Patients may not volunteer symptoms of PAD, and the ‘classical’ presentation of reproducible, exertional leg pain from intermittent claudication is often unrecognised. Many patients have their disease ‘masked’ because their

<table>
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<th>PAD stage</th>
<th>Symptoms</th>
<th>Clinical signs</th>
<th>Differential diagnosis</th>
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<tbody>
<tr>
<td>Asymptomatic or ‘masked’ PAD</td>
<td>Asymptomatic but with risk factors for PAD</td>
<td>Reduced or absent peripheral pulses</td>
<td>Mobility limitations due to other causes (sedentary lifestyle, musculoskeletal disease, comorbid illness such as heart failure, COPD)</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>Reproducible pain, cramping or fatigue in calf, thigh or buttock during exercise</td>
<td>Reduced or absent peripheral pulses</td>
<td>• Neurogenic claudication (eg nerve root entrapment, spinal canal stenosis) • Venous claudication (history of severe deep vein thrombosis or venous insufficiency) • Musculoskeletal causes (eg hip or knee osteoarthritis)</td>
</tr>
<tr>
<td>Chronic limb-threatening ischaemia</td>
<td>• Rest pain, especially with limb elevation • Nocturnal pain • Tissue loss: ulceration, gangrene, necrosis</td>
<td>• Absent peripheral pulses • Tropic changes (hair loss, muscle wasting, clawed toes) • Ulceration (punched out, sloughy, necrotic) • Gangrene (infection, blistering, abscess, skin breakdown) • Necrosis</td>
<td>• Venous ulceration • Malignant skin ulceration • Neurogenic related pain</td>
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**Table 1. Clinical presentation and differential diagnosis of peripheral artery disease stages**

COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease
walking is already limited as a result of other causes such as lumbar degenerative disease, including nerve root compression, hip and knee osteoarthritis, or frailty syndromes including cognitive impairment. Peripheral neuropathy from diabetes may mask painful ulcers or rest pain. Clinical history-taking and examination can be unreliable for diagnosing PAD if they are poorly performed.\(^{19}\)

CLTI presents with either rest pain or tissue loss (eg ulceration, gangrene and/or necrosis). CLTI affects approximately 1.2–2.0% of patients aged >40 years.\(^{12}\) Not all patients have a preceding history of intermittent claudication. Ulcers of the lower limb and foot require careful clinical assessment and further imaging to determine associated arterial causes. Concomitant venous disease or peripheral neuropathy can sometimes obscure the diagnosis of CLTI. Early recognition of CLTI and expedited referral to vascular surgery services is essential to improve limb salvage. In patients with diabetes and tissue loss, interdisciplinatory foot services reduce limb loss and improve healing.\(^1\) Hence, it is recommended all patients with diabetes-related foot ulceration have both a vascular surgical assessment and a high-risk foot service review.\(^1\)

Acute limb ischaemia (ALI) refers to the sudden occlusion of distal arterial perfusion and is usually due to thromboembolic events such as cardiac embolisation from atrial fibrillation, popliteal aneurysm thrombosis or hypercoagulable states. ALI is not included in the classification of PAD and is considered a separate pathological process to atherosclerotic PAD, especially as the underlying risk factors and prognosis are different. Patients report a history of sudden foot pain, pallor or coldness occurring over hours or days. Sensory loss or motor deficits signify an acutely threatened limb with limited viability. ALI requires urgent revascularisation because of the lack of peripheral collateral vessels. It is important to urgently transfer patients to the nearest emergency department with vascular services to avoid treatment delays that occur with outpatient imaging.

### Screening and diagnosis of PAD

ABI testing is useful as a screening investigation for high-risk patients and as a first-line diagnostic test for symptomatic patients.\(^2,^{24}\) The normal ABI range is 0.9–1.3.

### Table 2. Treatment recommendations for peripheral artery disease: Targeted secondary prevention

<table>
<thead>
<tr>
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<tr>
<td><strong>Smoking cessation(^1,^{2,3})</strong></td>
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<tr>
<td><strong>Antithrombotic (antiplatelet or anticoagulant) therapy</strong></td>
</tr>
<tr>
<td><strong>Antihypertensive therapy(^2,^{2,3})</strong></td>
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<tr>
<td><strong>Lipid-lowering therapy(^2,^{2,3})</strong></td>
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<tr>
<td><strong>Glycaemic control</strong></td>
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<td><strong>Diet and exercise</strong></td>
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\(\text{ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-receptor blockers; CLTI, chronic limb-threatening ischaemia; DOAC, direct-acting oral anticoagulant; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease; SGLT-2, sodium-glucose co-transporter 2}\)
An abnormal ABI has a high sensitivity/specificity for the presence of PAD. ABIs >1.4 indicate incompressibility of the arteries, which commonly occurs in patients with diabetes or chronic renal failure. ABI testing can be performed with a hand-held Doppler or automated ABI machine, but most accredited vascular laboratories provide ABI assessment.

There are no current Australian guidelines for population-based PAD screening. ABI screening of low-risk or asymptomatic patients in Australian general practice is not recommended because of limited supporting evidence.20 International guidelines recommend ABI testing to screen patients who are at high risk of PAD (as a result of comorbid disease, age or high cardiovascular risk).2,3 A number of barriers hinder the screening of high-risk or symptomatic patients with ABI in Australian primary care settings, which may explain why many patients undergo potentially unnecessary arterial duplex studies.21

For patients with symptoms of PAD and an abnormal ABI, further diagnostic imaging is indicated.1 Duplex ultrasonography is the first-line investigation, with stenosis >75% considered clinically significant. Computed tomography angiography is a second-line investigation reserved for when concerns about aortoiliac disease arise following ultrasonography or for operative planning. For patients with previous vascular intervention, symptom recurrence is typically investigated with duplex ultrasonography as a first-line investigation.2 There is a limited role for further imaging in patients with asymptomatic disease or in screening for PAD in other locations such as the carotid arteries, unless symptoms are present.2,20

Diagnosis of PAD presents an opportunity to initiate screening and review cardiovascular risk factors including blood pressure monitoring, lipid analysis and screening for diabetes and renal disease. History and examination can be used to screen for concomitant cardiac disease; if symptoms are present, further investigations can be arranged. Annual risk factor review including clinical assessment, routine blood profile, diabetes screening and lipid analysis is recommended for all patients with PAD.

**PAD treatment**

The treatment of PAD is guided by the disease severity (Tables 2 and 3). Traditionally, treatment focused on patients with symptoms of PAD (Table 3). With increasing understanding of the long-term morbidity and mortality consequences of PAD, a renewed emphasis on the importance of preventive therapy for asymptomatic patients is required (Table 2).

**Cardiovascular risk modification**

For all patients with PAD, treatment to address ongoing cardiovascular risk factors is essential. Smoking cessation, Table 3. Treatment recommendations for peripheral artery disease: Targeted lower limb treatments

| Interventions to improve mobility, reduce amputation risk and improve quality of life | Revascularisation surgery2,3 | Either open or endovascular therapy is recommended for all patients with CLTI. Revascularisation is considered for patients with severe, functionally limiting intermittent claudication and suitable operative risk factors. Endovascular surgery is considered first-line therapy for many patients requiring revascularisation; however, for low-risk patients with suitable anatomy, open surgery has superior long-term results.26 Revascularisation is not indicated for asymptomatic patients and may cause harm. |
| Exercise programs2,3 | Offer to patients with intermittent claudication or after endovascular therapy to improve walking distances and survival.21 Caution is recommended when prescribing exercise therapy for patients with CLTI; appropriate revascularisation and foot care is required as first-line therapy.1 |
| Pharmacotherapy for claudication2,3 | Pharmacotherapy for claudication with cilostazol or pentoxifylline has low-level evidence. Some patients with claudication may benefit from prescription. |
| Foot care1 | Patients with diabetes and PAD are at increased risk of diabetes-related foot ulceration. Perform regular 1–3-monthly foot checks during all routine clinical appointments. Include regular podiatry review in care plans to manage pre-ulcerative lesions such as heel callus, fissures or thickened nails as indicated. Therapeutic footwear and accommodative orthoses are recommended to be fitted by trained podiatrists, orthotists or pedorthotists. Early referral to both a vascular surgeon and specialised interdisciplinary care, such as a high-risk foot service, is recommended when tissue loss is identified. Arrange urgent hospital assessment for patients with diabetes and suspected sepsis due to foot ulceration. |

CLTI, chronic limb-threatening ischaemia; PAD, peripheral artery disease
blood pressure control, high-dose statins and antithrombotic treatment form the foundation of therapy (Table 2). Long-term outcomes related to mortality and lower limb events are improved with adherence to these four guideline-recommended treatments.3,22 Despite this, few patients are prescribed treatment according to guidelines, with population-based studies, both in Australia and internationally, showing that only approximately one-third of patients with lower limb arterial disease are optimised on appropriate medical therapies.18,22

Exercise programs for PAD
Exercise programs improve symptoms of intermittent claudication, reduce cardiovascular mortality, improve glycaemic control and decrease adverse lower limb events.2 Recent evidence shows that exercise programs also have significant benefit following endovascular interventions for PAD, with greater walking distances and improved QoL.23 Table 4 presents practical tips on how to structure a PAD-specific exercise program.

Endovascular and surgical treatments for patients with PAD
Surgery, either endovascular or open, is reserved for patients with severe, function-impairing claudication or CLTI.23 There is no strong evidence that surgical treatment prevents future amputation in patients without CLTI, and it may cause harm.2 Amputation rates are declining;24 despite this, long-term mortality remains high for all patients with PAD, primarily driven by cardiovascular death.

Endovascular therapy
Endovascular therapy has grown rapidly over the past few decades. In Australia, 70% of peripheral artery surgery in 2015 was endovascular, and the percentage continues to increase.24 Performing an endovascular procedure as the first-line revascularisation intervention is associated with increased survival and limb-salvage when compared with open surgery.25 In recent years, the disease complexity treated with endovascular surgery has improved as a result of advances in intervention techniques. Vascular surgeons employ a range of interventions, from balloon angioplasty or stenting to highly complex endovascular reconstructions that include atherectomy, or drug-eluting devices. The anatomical location of atherosclerotic lesions influences suitability for endovascular therapy, and it is important to recognise that some patients are best treated with open surgery.

Open surgery
Traditional methods of open surgery still have an important role in the treatment of PAD. For patients with lower operative risk, peripheral bypass with autologous vein offers superior long-term patency when compared with endovascular treatment.26 Additionally, for patients who have failed endovascular procedures, open surgery is critical for revascularisation and limb salvage.

Improving outcomes for patients with PAD in general practice
Patients with PAD have a complex array of health beliefs, symptoms and functional limitations. Surgical interventions have an important role in improving the QoL and functional limitations of patients with severe intermittent claudication and CLTI, but they are only part of the management algorithm. For significant improvements in long-term outcomes to occur in patients with PAD, the important part GPs play in early diagnosis, disease monitoring and risk factor management needs re-emphasis. Involving patients in setting treatment goals is important to ensure evidence-based management plans also address their specific goals. Fostering greater collaboration between GPs and vascular surgeons will encourage timely referrals, more prescription of secondary preventive medications, treatment adherence, exercise programs and support for smoking cessation. This continued emphasis on shared care relationships between all treating clinicians can assist with providing effective, person-centred care.

Key points
- PAD is common and associated with a significant risk of cardiovascular
mortality, stroke, acute myocardial infarction, and limb loss.

- Patients with asymptomatic disease or intermittent claudication have a low overall risk of amputation but considerable cardiovascular risk.

- Tissue loss (arterial ulcers, gangrene and/or necrosis) indicates CLI and confers a very high risk of limb loss, and mortality. Expeditied referral for vascular surgical review and consideration of revascularisation for all patients with CLI can improve limb salvage.

- Non-surgical management is focused on risk factor modification, with smoking cessation; antithrombotic, antihypertensive, and statin medications; and exercise therapy. Consideration of polyvascular disease and active management of cardiovascular risk factors can reduce the mortality risk for patients with PAD.

- Greater partnership between GPs and vascular surgeons can help improve outcomes for patients with PAD.

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References


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